Long-Term Surveillance of Ground-Glass Nodules

Evidence from the MILD Trial

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Introduction: The purpose of this study was to evaluate the natural evolution of ground-glass nodules (GGNs) in the Multicentric Italian Lung Detection (MILD) trial, which adopted a nonsurgical approach to this subset of lesions.

Methods: From September 2005 to August 2007, 56 consecutive MILD participants with 76 GGNs were identified from 1866 individuals who underwent baseline low-dose computed tomography. The features of GGNs were assessed and compared with the corresponding repeat low-dose computed tomographies after a mean time of 50.26 ± 7.3 months. The GGNs were classified as pure (pGGN) or part-solid (psGGN) GGNs. The average of the maximum and the minimum diameters for both pGGNs and psGGNs and the maximum diameter of the solid portion of psGGNs were manually measured. At follow-up, GGNs were classified as follows: resolved, decreased, stable, or progressed (according to three defined growth patterns).

Results: A total of 15 of 48 pGGNs (31.3%) resolved, 4 of 48 (8.3%) decreased in size, 21 of 48 (43.8%) remained stable, and 8 of 48 (16.7%) progressed. Among the psGGNs with a solid component smaller than 5 mm, 3 of 26 (11.5%) resolved, 11 of 26 (42.3%) remained stable, and 12 of 26 (46.2%) progressed. One of the two psGGNs with a solid component larger than 5 mm remained stable, and the other decreased in size. Four lung cancers were detected among the GGN subjects, but only one arose from a psGGN, and was resected in stage Ia.

Conclusions: The progression rate of the GGNs toward clinically relevant disease was extremely low in the MILD trial and supports an active surveillance attitude.

Key Words: Ground-glass nodule, Lung cancer screening, Long-term surveillance.

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Subsolid lung nodules, also termed ground-glass nodules (GGNs), are often encountered during computed tomography (CT) examinations for lung disease. They may represent a variety of disorders ranging from inflammatory abnormalities to lung neoplasms, and may indeed show different evolution over time.[1–3] If it is true that some GGNs may be stable over time and more likely represent malignant or premalignant abnormality, a substantial proportion of them are instead transient.[4–6] Indeed, despite the increased understanding during the last decade of the varieties of the GGNs, these lesions continue to represent a challenging task for clinicians, surgeons, and radiologists.

The difficulty in the management of the GGNs is particularly evident in the lung cancer screening setting, partly because of the scarce information on these entities at the time in which multicentric randomized trials were designed.[7,8] Furthermore, there are important data consistent with the notion of overdiagnosis occurring in a considerable percentage of screening-detected lesions.[9–11] However, the nonuniform management strategies for these lesions across the lung cancer screening trials may give the possibility of achieving additional important information in this regard.

Thus, the purpose of this study was to evaluate the evolution of the GGNs in the Multicentric Italian Lung Detection (MILD) trial, which adopted a very conservative, nonsurgical approach to this subset of lesions.

PATIENTS AND METHODS

Study Population

The study population comprised all the consecutive patients who underwent baseline low-dose (LD) CT (LDCT) examination between September 2005 and August 2007 (n = 1866, 1280 men, 68.6%, and 586 women, 31.4%; mean age 57.6 ± 4.8 years) as part of the MILD project at the National Cancer Institute of Milan. The MILD project is an ongoing multicentric population-based randomized, controlled, lung cancer screening trial, and its primary aim is the impact of early lung cancer detection on mortality. The MILD project was approved by the Institutional Review Boards, and written informed consent was obtained from all participants. For this substudy, the original Institutional Review Boards' approval and informed consent allowed use of data for future research.

Part of the study subjects had been included in other studies addressing a separate hypothesis.[12,13] Eligibility criteria for the MILD included: 49 to 75 years of age, current or former smokers (having quit smoking within 10 years before recruitment) with at least 20 pack-years of smoking history and no history of cancer within the previous 5 years. Details of MILD eligibility criteria, randomization protocol, lung nodule detection, and management protocol have been previously described.[12]

LDCT Technique

LDCT was performed by using a 16-detector row CT scanner (Somatom Sensation 16, Siemens Medical Solutions, Forchheim, Germany). All LDCT scans of the whole lung were acquired during one deep inspiratory breath-hold without the use of the contrast medium. Standard LDCT parameters were as follows: 120 kV, effective 30 mAs, individual detector collimation 0.75 mm, gantry rotation time 0.5 second, pitch 1.5. LDCT images for the lung nodule detection were reconstructed as follows: 1-mm–thick sections with a reconstruction increment of 1 mm (medium-sharp kernel - B50f).

Original MILD Management of the GGNs

Using defined criteria, radiologists working for the MILD trial (MILD readers) were asked to report the presence of any pure (pGGN) and part-solid (psGGN) GGNs. According to the MILD protocol, both pGGNs and psGGNs with a solid component smaller than 5 mm had to be followed up regardless of their size and their number (i.e., single or multiple). These subjects were scheduled for repeat LDCT scanning according to both their LDCT arm of randomization and other lung findings.[12] Only the psGGNs with a solid component larger than 5 mm were considered suspicious for malignancy and indeed followed up at 1 year (if sized 5 to 8 mm) or evaluated by positron emission tomography (PET) scanning and invasive diagnostic procedures (if sized more than 8 mm) as jointly established by the senior MILD radiologist (AM) and the thoracic surgeon (UP) coordinating the MILD trial.

Radiologic Assessment of the GGNs by Core Readers

For the present study, all the LDCTs were reviewed on three different personal computers running a Dicom viewer software validated for clinical purpose (OsiriX, 3.5.1 Imaging Processing Software, 64-bit format, Pixmeo SARL, Bernex, Switzerland) by three readers (*core readers)* as follows: MS, CM, and GN reviewed 1203, 483, and 200 LDCT scans, respectively. The core readers were in the course of their training as thoracic radiology subspecialists at the Academic Hospital of Parma and they had 2 years' experience in interpreting thin-section CT scans. The core readers were blinded to the original interpretations by the MILD readers. They received specific training, which consisted of viewing a slide presentation that defined and showed examples of lesions having various features and understanding the current literature.

In cases of uncertain diagnosis, the core readers were instructed to classify the corresponding LDCT findings as positive, because these would have to be reviewed with a chest radiologist (NS with 5 years of experience in interpreting LDCTs lung cancer screening) who would then decide to maintain or discard the evaluations of the core readers. Subsequently, the core readers and the chest radiologist jointly classified each selected GGN as pGGN or psGGN.

Both baseline and the latest corresponding follow-up LDCT were evaluated for the GGNs measurements only by one of the three core readers (MS). For the pGGNs, both the maximum length and the width (defined as the longest diameter perpendicular to length on the same CT image) were measured. The GGN size was defined as the average of these two measurements.[14] For the psGGNs, the maximum length of the solid component was also measured. Measurements were manually determined using the electronic caliper. All these measurements were also repeated after 4 months by another core reader (CM) to evaluate the interobserver variability. Then, the core readers, the chest radiologist, and one thoracic surgeon coordinating the MILD trial reviewed in consensus both the baseline and the latest follow-up LDCT images to evaluate any change in attenuation (e.g., development of any solid component within a pure GGN) of the GGNs.

Data Analysis

At follow-up LDCT, each pGGN was classified as follows: resolved, decreased (by at least 2 mm as compared with the same nodule at baseline LDCT), stable, or increased (by at least 2 mm as compared with the same nodule at baseline LDCT). The development of a solid component within a pGGN was also considered a sign of progression/malignancy. Similar criteria were applied to psGGNs as follows: decreased (if the solid component alone or along with the total average size by at least 2 mm as compared with the same nodule at baseline LDCT), stable (including no variation of the solid component associated with a decrease of the total average size), and increased. The increase of the GGNs was subclassified into three growth patterns: (1) an increase by at least 2 mm of the solid component (Fig. 1*A*); (2) an increase by at least 2 mm of the total average size (Fig. 1*B*); and (3) an increase of both the solid component and total average size of at least 2 mm (Fig. 1*C*). The 2-mm threshold was based on intraobserver variation data reported by a prior study.[15]

Evolution of the GGNs was stratified either by the MILD original classification system (i.e., pGGNs, psGGNs with a solid component < 5 mm, and psGGNs with a solid component > 5 mm) or by the interim guidelines proposed by Godoy et al.[8] as follows: solitary pGGNs with the maximum diameter smaller than 5 mm, solitary pGGNs between 5 and 9 mm, solitary pGGNs larger than 10 mm, solitary psGGNs of any size, and multiple GGNs. To determine variability, we calculated the 95% confidence interval (CI) for the limits of agreement by using Bland-Altman analysis.[16] Normally distributed data are shown as means ± SD. p Values of less than 0.05 were considered to indicate statistical significance.

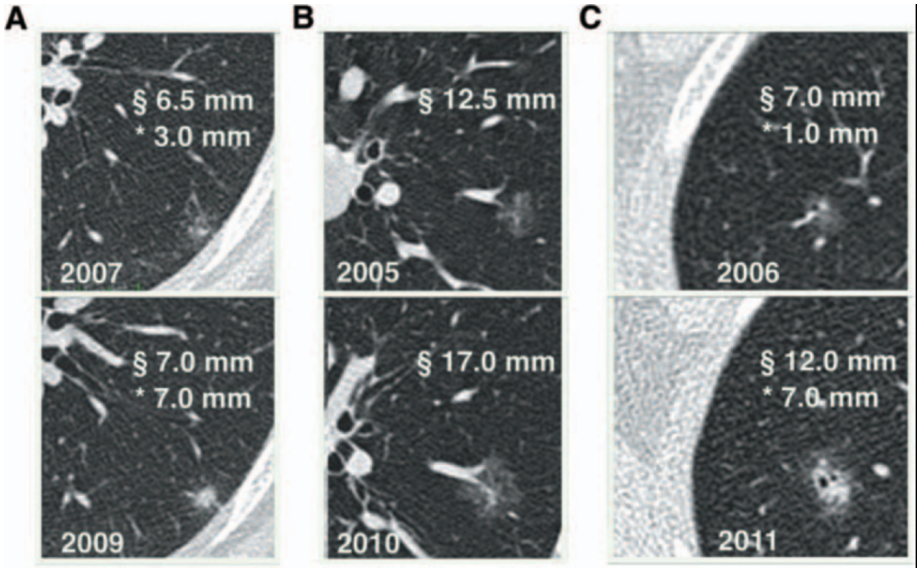

FIGURE 1. *A*, Growth pattern 1: increase of the sole solid component. Any increase or decrease in size is defined as a variation of at least 2 mm. *B*, Growth pattern 2: increase of the total average size.Any increase or decrease in size is defined as a variation of at least 2 mm. *C*, Growth pattern 3: increase of both the solid component and total average size. Any increase or decrease in size is defined as a variation of at least 2 mm. * indicates solid component; §, average size.

TABLE 1. Evolution of the Ground-Glass Nodules According to the Mild Protocol

		psGGNs	
	pGGNs	**With a Solid Component < 5 mm**	**With a Solid Component > 5 mm**
Baseline	48 (6.7 ± 1.9 mm)	26 (7.4 ± 1.9 mm)	2 (8.5 ± 2 mm)
Resolved at follow-up	15	3	0
Decreased in size at follow-up	4 (−4.25 ± 0.75 mm)	0	1 (0.5 mm)[a] (−12 mm)[b]
Stable at follow-up	21 (0.07 ± 0.71 mm)	11 (0.17 ± 1.86 mm)[a] (0.09 ± 0.83 mm)[b]	1(0.5 mm)[a] (0 mm)[b]
Grown at follow-up			
Pattern 1	0	3 (0.5 ± 0.33 mm)[a] (4.67 ± 1.78 mm)[b]	0
Pattern 2	7(4.42 ± 0.61 mm)	5[c] (3.4 ± 0.32 mm)[a] (0.4 ± 0.48 mm)[b]	0
Pattern 3	1[d] (6.5 mm)[b]	4(3 ± 1 mm)[a] (3.75 ± 1.75 mm)[b]	0

[a]Average size.
[b]Solid component.
[c]One lung cancer arose from one psGGN showing a growth pattern 2.
[d]Newly developed solid component.
pGGN, pure ground-glass nodules; psGGN, part-solid ground-glass nodules.

RESULTS

At baseline, the core readers identified 76 GGNs in 56 of 1866 MILD participants (3%) (30 men, 53.6%, and 26 women, 46.4%; mean age 59.7 ± 5.2 years). The MILD readers had originally identified 11 of 1866 subjects (0.6%) with 13 GGNs, which were then all detected by the core readers.

At baseline, the mean size of the GGNs was 6.97 ± 2 mm. Forty-four participants (78.6%) had a solitary GGN, whereas 12 participants (21.4%) had multiple GGNs as follows: two in eight subjects (14.3%), three in two (3.6%) subjects, and five in two subjects (3.6%). A total of 48 of 76 (63.2%) were pGGNs (6.7 ± 1.9 mm), whereas 28 of 76 (36.8%) were psGGNs (7.5 ± 1.9 mm). Only two of 28 psGGNs (7.1%) displayed a solid component larger than 5 mm, of 7 mm and 12 mm, respectively. Both these lesions were identified either by the core or the MILD readers.

For the manually measured GGN size, the 95% CI for the limits of agreement was −1.9, 2.2 mm for interobserver variability at baseline and −2.1, 2.2 mm for interobserver variability at follow-up. For the solid component diameter,

TABLE 2. Evolution of the Ground-Glass Nodules According to the Interim Guidelines

	Solitary GGNs				Multiple GGNs		
	pGGNs <5 mm	pGGNs 5–9 mm	pGGNs >10 mm	psGGNs	pGGNs <10 mm	pGGNs ≥10 mm	psGGNs
Baseline	0	26 (6.3 ± 1.0 mm)[a]	4 (14.5 ± 3.5 mm)[a]	14 (8.7 ± 2.9 mm)[a] (3.6 ± 1.9 mm)[b]	13 (6.2 ± 1.4 mm)[a]	5 (12.0 ± 1.6 mm)[a]	14 (8.1 ± 2.0 mm)[a] (2.4 ± 1.1 mm)[b]
Resolved at follow-up	0	6	2	0	6	1	3
Decreased in size at follow-up	0	0	1 (−8 mm)[a]	1 (0 mm)[a] (−12 mm)[b]	2 (−4.5 ± 1.5 mm)[a]	2 (−3.0 ± 1.0 mm)[a]	1 (0.0 mm)[a] (−2.0 mm)[b]
Stableat follow-up	0	17 (−0.1 ± 0.6 mm)[a]	0	7 (−0.86 ± 2.12 mm)[a] (0.43 ± 0.53 mm)[b]	2 (0.0 ± 0.0 mm)[a]	0	1 (1.0 mm)[a] (0.0 mm)[b]
Grown at follow-up							
Pattern 1	0	0	0	3 (0.7 ± 0.4 mm)[a] (3.3 ± 1.8 mm)[b]	0	0	1 (−1.0 mm)[a] (6.0 mm)[b]
Pattern 2	0	3 (3.7 ± 0.9 mm)[a]	1(3 mm)[a]	3 (2.7 ± 0.4 mm)[a] (0.0 ± 0.0 mm)[b]	2 (5 ± 3 mm)[a]	2 (5.0 ± 1.0 mm)[a]	5[c] (4.0 ± 0.8 mm)[a] (0.4 ± 0.5 mm)[b]
Pattern 3	0	0	0	0	1 (6 mm)[a] (5 mm)[b]	0	3 (5.3 ± 2.2 mm)[a] (4.3 ± 01.8 mm)[b]

[a]Average size.
[b]Solid component.
[c]One lung cancer arose from one psGGN showing a growth pattern 2.
[d]Newly developed solid component.GGNs, ground-glass nodules ; pGGN, pure ground-glass nodules; psGGN, part-solid ground-glass nodules.

the 95% CI for the limits of agreement was −1.6, 1.5 mm for interobserver variability at baseline and −2, 1.9 mm for interobserver variability at follow-up.

The majority (47 of 76, 61.8%) of the GGNs were identified in the upper lobes. Specifically, the GGN distribution was as follows: 25 GGNs (32.9%) in the right upper lobe, 24 GGNs (31.6%) in the left upper lobe, 13 GGNs (17.1%) in the right lower lobe, nine GGNs (11.8%) in the left lower lobe, and five GGNs (6.6%) in the middle lobe.

The evolution of the GGNs after a mean follow-up of 50.26 ± 7.3 months is summarized in Table 1. A total of 15 of 48 pGGNs (31.3%) completely resolved (mean follow-up of 44.68 ± 10.53 months), four of 48 pGGNs (8.3%) decreased in size (−4.25 ± 0.75 mm after a mean follow-up of 52.67 ± 6.18 months), 21 of 48 pGGNs (43.8%) remained stable (mean follow-up time of 53.02 ± 6.78 months), and eight of 48 pGGNs (16.7%) increased in size (4.1 ± 1.8 mm, 50 ± 0.2% after a mean follow-up of 55.53 ± 6.47 months). Only one pGGN developed a solid component of 5 mm after 63.9 months; this patient, however, arbitrarily abandoned the screening program after the last follow-up LDCT examination. Three patients with pGGNs also underwent PET-CT scanning because of the presence of one solid lesion located in the same lobe of the pGGN. Two of these solid nodules were positive at PET-CT scanning; of these, one resulted in a stage Ia adenocarcinoma and the other resulted in a pleural adenocarcinoma after surgery.

A total of three of 26 psGGNs (11.5%) completely resolved in two subjects (mean follow-up of 54.54 ± 2.73 months), whereas 11 of 26 psGGNs (42.3%) were stable (mean follow-up of 53.7 ± 5.4 months). One baseline psGGNs with a solid component of 12 mm was negative at PET-CT scanning and lost its solid component after 54 months, thus transforming into a pGGN. The other lesion with a solid component of 7 mm at baseline was only followed up and remained stable after 51 months. The majority of the remaining psGGNs (i.e., with a solid component < 5 mm at baseline) progressed in nine subjects (mean follow-up of 52.11 ± 3.9 days). Specifically, a growth pattern 1 (mean increase of the solid component 4.67 ± 1.78 mm) was recorded in three of 26 psGGNs (11.5%), a growth pattern 2 (mean increase of the average size 3.4 ± 0.32 mm) was recorded in five of 26 psGGNs (19.2%), whereas a growth pattern 3 (mean increase of the average size 3 ± 1 mm; mean increase of the solid component 3.75 ± 1.75 mm) was observed in four of 26 psGGNs (15.4%).

A total of eight subjects with at least one psGGN underwent PET-CT scanning. Specifically, two of eight subjects (25%) underwent PET-CT scanning because of a coexisting solid nodule in a different lobe of the stable psGGN (average size 4.75 ± 0.25 mm; solid component 2.5 ± 0.5 mm). In these cases, both psGGNs and solid nodules were negative on PET-CT. The remaining six of eight cases (75%) had a growing psGGN: one psGGN (average size 11 mm; solid component 10 mm) positive on PET-CT turned out to be a stage Ia pulmonary adenocarcinoma after surgery; one psGGN (average size 12.5 mm; solid component 10 mm) negative on PET-CT was associated with a positive concomitant solid nodule in a

different lobe, which resulted a stage IV pulmonary neuroendocrine tumor after surgery; the remaining four growing psGGNs (average size 11.75 ± 2.95 mm; solid component 8.75 ± 1.49 mm) were negative on PET-CT. One subject with a growth pattern 2 psGGN did not undergo PET-CT scanning and is still under evaluation.

According to the interim guidelines, a total of five of 18 multiple pGGNs (27.8%) and four of 30 solitary pGGNs (13.3%) increased in size at follow-up. The proportion of increasing psGGNs was similar between solitary and multiple lesions (Table 2).

DISCUSSION

This study shows a variable evolution for the GGNs at long-term follow-up. Our findings increase the current concerns about the optimal balance between the need for a prompt surgical intervention for invasive lung cancer and the need to limiting overtreatment for indolent disease.

First, we found that the most GGNs were originally overlooked by the MILD readers. The discrepant detection rate between the MILD and the core readers is in keeping with prior studies reporting a sizeable nodule miss rate in the screening setting.[17,18] The main concern of identifying all noncalcified solid nodules and the scarce understanding of GGNs at the time in which the study cases were originally interpreted by the MILD readers might have increased the subsolid nodule miss rate. Second, the MILD criteria—only psGGNs with a solid component larger than 5 mm or pGGNs developing a solid component over time were considered suspicious for malignancy—might have led the MILD readers to be less careful in reporting other GGNs. Nevertheless, all the psGGNs with a solid component larger than 5 mm were identified by the MILD readers.

According to the MILD protocol, both pGGNs and psGGNs with a barely measurable solid component were regarded unworthy of any immediate surgical intervention. They were considered as pre- or low-grade neoplastic forms that might represent overdiagnosis of lung cancer—that is, that it progresses so slowly as to be inconsequential—or represent inflammatory changes in their vast majority. Despite its questionability, such a conservative management has allowed the evaluation of the natural course of these lesions. To our knowledge, no other lung cancer screening trial has described the evolution for the whole spectrum of the GGNs for such a long-term follow-up.

We observed that combined resolving, decreasing in size and stable nodules (54 of 76, 71.1%) constituted the majority of the GGNs. In our study, the frequency of transient GGNs (23.7%) was lower than that reported by previous studies (37–70%) despite the longer follow-up.[5,6,19] Transiency was more frequently observed among pGGNs as compared with psGGNs, whereas a large solid portion was an independent predictor of transiency in a prior investigation.[6] Of note, the few resolving psGGNs were observed only when they were multiple. Such a difference with prior investigations might be explained by several factors such as the different participants' eligibility criteria. For example, the study population evaluated by Lee et al.[6] was more heterogeneous for both smoking history (as never smokers were also included) and age range (26–79 years) as compared with the study population of MILD. Besides, we have evaluated only the GGNs detected at baseline, whereas those detected at follow-up proved more likely to be transient in the study by Lee et al.[6] Our findings are in keeping with those of other studies that showed that the larger the solid component, the greater the likelihood it was proved to be not transient.[20]

We found that the majority of the pGGNs remained stable over time. Although the stratification of the pGGNs according to their size may be useful to decide the best approach to each subset of lesions, our data cannot provide any evidence in this regard because of the small number of cases whose size was smaller than 5 mm and larger than 10 mm. However, even some pGGNs increased in size, particularly when they were multiple. In addition, two cases developed a solid tumor in the same lobe of the pGGN. A bit surprisingly, we found that only one pGGN developed (after 63.9 months) a newly solid component that, however, could not be further investigated as that participant arbitrarily abandoned the screening. Therefore, our findings are in keeping with previous observations suggesting that traditional follow-up periods of 2 or 3 years may be insufficient to safely diagnose benign disease for the pGGNs.[8,21]

We found that decreased-in-size nodules represented the minority of cases. However, it should be taken into account that some tumors may show an irregular growth pattern, which includes a decrease in size at some time point.[20] In our view, a longer follow-up period is needed to understand the nature of these GGNs because lung surgery is not warranted for decreased in size lesions.

The finding that nearly half (46.2%) of the psGGNs increased in size is consistent with the greater likelihood of malignancy or premalignancy for this subset of lesions. In a study by Li et al. [21] 69% of lung cancers missed by radiologists at screening CT were found to be psGGNs. A substantial delay in biopsy was also reported by the New York Early Lung Cancer Action Project study for 10 cancers that manifested as psGGNs or pGGNs at baseline.[7] In one case in the present study cohort, an immediate resection of a solitary psGGN would have probably hampered the surgical treatment of a large solid tumor that occured later in the contralateral lung.

The MILD strategy entailing the selective use of PET-CT for the evaluation of the psGGNs may be questionable because of the PET high false-negative rate for identifying neoplastic GGNs.[22–24] However, in more than 10 years of systematic use of PET in lung cancer screening, we have not experienced any relevant diagnostic problem. In fact, false-negative PET invariably represents slow-growing disease that can be monitored for growth assessment and eventually resected in early stage. Conversely, the quantification of PET standard uptake value might provide useful information on the biologic features of CT-detected lesions, and also disclose which multiple lesions should be resected.[8]

All measurements were obtained manually and were indeed subject to interobserver variability. In a post hoc analysis, we found that the levels of interobserver variability for measurements of the solid component and the global size of the GGNs were similar to those reported by De Hoop et al.[15] As proposed by the same authors, the use of a change in lesion

mass proved to be more accurate than simple measurements of lesion diameter by the electronic caliper, resulting in markedly improved inter- and intraobserver agreement and a substantial decrease in the time necessary to detect interval growth.[15] Future studies assessing GGNs mass changes over time are needed to further explore this topic.

This study has several limitations. A number of the pulmonary nodules detected in our study are currently being followed up, and the verified diagnostic outcome (pathology or otherwise) for most subjects is unavailable. Nevertheless, the observation that no GGN progressed into a clinical disease or increased in size so rapidly to hamper any curative lung resection provides further information on the natural evolution of these subtypes of lesions. In line with our findings, Sawada et al.[22] suggested that long follow-up period for lung cancer presenting as GGN did not cause any important treatment delay and did not negatively influence the final outcome.

By classifying the GGNs according to the interim guidelines we found that 29 of 56 subjects (51.8%) should have undergone surgical resection. Such a high proportion adds further questions on the optimal management of GGNs in the screening programs, facing two major issues: unnecessary treatment of indolent tumors or benign abnormalities because of overdiagnosis on the one hand, and the need of resecting potentially aggressive lung tumors earlier on the other hand. Although we cannot draw any conclusions on the optimal management of the GGNs, the conservative MILD approach to GGNs was also rewarded by the lower proportion of invasive procedures that revealed benign disease as compared with other screening results (9% versus 27.2%).[23] Furthermore, we did not specifically address the issue of the GGNs features that best predict their evolution as this was beyond the scope of the present study and it was already explored by previous investigations.[27, 28] It is also worth emphasizing that our data were observed across a study cohort of current or former smokers recruited by a lung cancer screening trial and evaluated by a specific CT protocol. Therefore the conservative management of the GGNs suggested by our study might not apply to patients evaluated in routine practice. Further studies are needed to evaluate the evolution of the GGNs out of the screening context and to standardize the CT technique for it.

In conclusion, by providing a large snapshot of the natural evolution of different GGNs, our study indicates the lack of clinical disease progression of these entities, and supports an active surveillance attitude.

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